Collateral impact: a dual role for climbing fibre collaterals to the cerebellar nuclei?

Jasmine Pickford and Richard Apps

School of Physiology, Pharmacology and Neuroscience, University of Bristol

Corresponding author: Richard Apps (r.apps@bristol.ac.uk)
School of Physiology, Pharmacology and Neuroscience
University of Bristol
Biomedical Sciences Building
University Walk
Bristol
BS8 1TD

The principal source of synaptic inputs to the cerebellum arise from mossy fibres and climbing fibres (CFs). Both types of afferent innervate Purkinje cells of the cerebellar cortex – mossy fibres indirectly via the granule cell-parallel fibre pathway and CFs directly from the inferior olive. Both afferents also have axon collaterals targeting the cerebellar nuclei (CN). The latter are responsible for cerebellar output which influences multiple brain structures involved in functions ranging from movement control to cognition.

The CF input to Purkinje cells is one of the strongest synapses in the mammalian nervous system and CF signals are generally thought to be central to cerebellar function. However, little is known about the physiology of olivocerebellar (CF) collateral connections to the CN.

The rodent cerebellum continues to develop in the first three postnatal weeks, during which time the CF system is extensively refined in the cerebellar cortex. Initially, each Purkinje cell is innervated by multiple CFs, however only one CF input is strengthened while others are eliminated, so that in the fully developed cerebellum each Purkinje cell is innervated by a single CF (Watanabe & Kano, 2011). In their recent study, Najac and Raman (2017) investigated CF collateral inputs to the CN during a similar time period and found that CF collaterals provide strong synaptic input to the CN during early development.

An elegant optogenetic approach was used to selectively stimulate CF collaterals *in vitro* in mice, allowing CN responses to CF collateral activation to be studied without contamination by other synaptic inputs (including mossy fibre collateral synaptic contacts which greatly outnumber CF collaterals). Selectivity was achieved by targeting viral injections into the inferior olive - the sole origin of CF collaterals and CFs. As a result, olivocerebellar axonal projections were selectively transfected with light-sensitive channelrhodopsin. Optical activation of collateral terminals within the CN revealed systematic changes in excitatory postsynaptic currents recorded from CN neurons during development - these currents were three-fold larger in young mice (P12-14) compared to those recorded in adults (~P60).

This substantial change in synaptic efficacy suggests that CF collaterals may play different roles in the juvenile and adult cerebellum. In the first few postnatal weeks CF collateral inputs to the CN are refined in parallel with CF pruning in the cerebellar cortex. Najac and Raman (2017) estimate that the degree of convergence of CF collaterals on each CN neuron decreases from ~40 in juvenile mice to ~8 in adult mice, and it is this reduction in number of inputs which mainly produces the corresponding reduction in synaptic strength in adult animals. This, in turn, may underlie the formation of olivo-cortico-nuclear loops which are widely thought to represent the basic operational units of the adult cerebellum.

Previous anatomical and physiological mapping studies in mature animals (e.g. Andersson & Oscarsson, 1978; Cerminara *et al.*, 2013) have shown that a key organising principle of cerebellar circuitry is such that CFs arising from specific olivary subdivisions target Purkinje cells in the contralateral cerebellar cortex that are arranged into longitudinally orientated microzones of 0.2-0.3 mm in mediolateral width. Purkinje cells located within each cortical microzone provide a highly convergent projection to CN neurons located within specific territories within the cerebellar and vestibular nuclei, thereby forming a series of highly topographically organised olivo-cortico-nuclear circuits (for review see Apps & Hawkes, 2009). Further anatomical order is imposed as a result of collaterals from the input stage of the circuit, providing synaptic input to the same CN neurons, and a subset of CN neurons providing an inhibitory feedback to the originating olivary subnucleus. The pruning of CF collaterals during postnatal development may therefore reflect the refinement of cerebellar microcircuitry into well-defined functional units.

Najac and Raman (2017) also found that CF collateral activation evoked substantial synaptic responses in the CN in adult mice, indicating that such inputs are likely to continue to have an important role in the fully developed cerebellum. The excitatory postsynaptic currents showed multiple peaks due to burst firing in olivary afferents with varying latencies. The number of CF axonal spikes in each burst has previously been shown to depend upon subthreshold oscillations in the inferior olive, allowing information content in CF synaptic inputs to Purkinje cells (Mathy *et al.*, 2009). This in turn may be important in various functions including synaptic plasticity. In the adult cerebellum CF collateral inputs to the CN may therefore play a similar role: providing graded information to the CN dependent upon the state of the inferior olive. This could alter the probability of inducing various cellular responses including, for example, those required for long-term plasticity.

The study by Najac and Raman (2017) therefore raises the intriguing possibility that CF collaterals to the CN in the juvenile and adult cerebellum serve different functional roles: during early postnatal development CF collaterals may play a role in sculpting cerebellar functional microcircuits, while in the adult they may play a role in providing information about olivary state.

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